Applicants hereby submit a version with markings to show changes made:

3. (Amended) The process of claim 1 where the polymer is selected from the group consisting of imidazole groups, pyridine groups, or aniline groups.

REMARKS

Drawings:

1. Applicants acknowledge that the drawings submitted have been approved.

Double Patenting:

2-5. Applicants will file a terminal disclaimer upon allowance.

Rejection under 35 USC 112:

6-7. Claim 3 is rejected under §112, second paragraph.

Applicants have amended claim 3 as suggested in the Action. The rejection is believed to be obviated.

Rejection under 35 USC 102:

8-9. Claim 1 is rejected under §102 as being anticipated by US 5,698,531. The Action states that the '531 patent teaches a process for delivering a polynucleotide complexed with a polymer into an extravascular parenchymal cell of a mammal. Applicants respectfully disagree.

Applicants believe that the '531 patent is not enabling for delivery of polynucleotides to cells and especially non-endothelial cells and therefore does not "teach" their processes.

The Nabel et al. prior art cited in the Office Action has not shown delivery and expression of a naked DNA to a parenchymal cell. The delivery of naked DNA to cells outside of the blood vessel is not taught by Nabel et al. For example, in the '531 specification, there is one example (beginning in column 15, line 55) of endothelial cells being removed from a minipig, transfected with a virus *in vitro*, and instilled into the endothelium of the iliac artery by injection from a double balloon catheter. The balloons were used to denude (scrape) the vessel inner wall so that the transfected cells would stick. Expression was found in the endothelial cells in and near the denuded arterial wall.

To put the one example into perspective: there are two columns in the specification devoted to the example; the first fourteen and one-half columns contain a discussion of ideas and possibilities. The Federal Circuit has repeatedly held that the specification must teach those skilled in the art how to make and use the invention without 'undue experimentation'." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The '531 specification contains lists of potential occurrences and future possibilities but does not teach how to deliver a polymer complex to an extravascular cell.

The following quotation was taken from a review article written by E. Nabel where she cited other Nabel et al. published articles: Circulation, 91:541-548 (1995), pg 543, col. 2, last paragraph: "Several observations concerning the delivery of recombinant genes and patterns of gene expression can be drawn from these studies. Infusion of vector into normal arteries with an intact endothelium results in transfection of intimal cells (primarily endothelial cells). Injury to the vessel and/or application of pressure to the vector infusate results in delivery of DNA transmurally and gene expression in the media." Applicants point to the specific limitations in scope that the author places on the extent to the types of cells that are transfected using the '531 processes.

In J Clin Invest. 1996 Jul 1; 98(1):225-35, Gary Nabel writes "Injury to atherosclerotic arteries induces the expression of growth regulatory genes that stimulate cellular proliferation and intimal formation. Intimal expansion has been reduced *in vivo* in nonatherosclerotic balloon-injured arteries by transfer of genes that inhibit cell proliferation. It is not known, however, whether vascular cell proliferation can be inhibited after injury in more extensively diseased atherosclerotic arteries. Accordingly, the purpose of this study was to investigate whether expression of recombinant genes in atherosclerotic arteries after balloon injury could inhibit intimal cell proliferation."

Both Gary and Elizabeth Nabel are authors of the following statement in 1997, six years after their '531 application was filed (bold type added): "Although gene delivery to the pulmonary circulation has both experimental and therapeutic potential, **the delivery methods**, distribution of transgene, and subsequent inflammatory response **have been poorly characterized to date** ... This technique should prove useful for investigations requiring over expression of novel genes in the pulmonary artery wall, and could ultimately be used to develop gene-based therapies for pulmonary vascular diseases." (Am J Respir Cell Mol Biol 1997 Jun;16(6):640-9).

It is clear from the '531 inventor's statements (after the filing date) that vessel wall transfection using balloon injury is their area of interest. To this date, Applicants have not found any references by the Nabels that describe delivery and expression beyond vessel walls. To infer enablement and teaching from the language in the '531 patent for anything other than vessel wall delivery is not reasonable based upon the

inventor's subsequent record.

Conversely, Applicants have shown delivery of polynucleotide complexes to cells beyond vessel walls. Applicants' delivery method does not require a catheter nor does the method involve Nabel-like "injury" to the vessel wall. Applicants' insertion of complex can be from a point away from the intended delivery area. All of these are significant advances over Nabel et al. delivery methods.

In addition to the foregoing discussion, the specification of a patent must teach the method relied upon in the Office Action in a way that would allow a person having ordinary skill in the art to use the method. The mere mention of a possible method is not considered teaching the method. In Genentech Inc. V. Nordisk A/A, 42 USPQ2d 1001 (CAFC, 3/13/97) the specification describes three or four applications for which cleavable fusion expression is well-suited. The Federal Circuit ruled that such statements do not describe specific material or any reaction conditions and therefore do not teach. The Court stated on page 1005 that tossing out the mere germ of an idea does not constitute a teaching.

Similarly, the '531 patent merely mentions possibilities for delivery without showing how to achieve it. It is clearly unreasonable to expect a scientist in the field to deliver and express a polynucleotide complex to an extravascular cell with direction provided by the simplistic statements found in the '531 specification. The amount of direction presented and the number of working examples provided in the specification are very narrow. The vascular type of gene delivery technology was unpredictable at the time, and the amount of experimentation required to adapt cell delivery to a vascular wall to polynucleotide delivery to an extravascular cell was quite high, especially in light of the record. Thus, the teachings set forth in the specification provide no more than a list of possibilities.

Rejection under 35 USC 103:

10-12. Claims 1-3 are rejected under 35 U.S.C. §103(a) as being unpatentable using US 5,698,531 along with US 2001/0005717.

Applicants respectfully disagree and rely on the §102 discussion to over come this §103 rejection.

Applicants believe that they have overcome the rejections in the Office Action. Claim 3 has been amended to be placed in allowable condition.

If the Examiner would like more information or has any questions, please feel free to contact me.

Respectfully submitted,

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I hereby certify that this correspondence is being sent by facsimile transmission to art unit 1636, 703.308.4242: Commissioner for Patents, Washington, DC on Thursday, October 10, 2002.

Signature